AIDS Vaccine 06
www.aidsvaccine06.org

An HIV Vaccine: Will it Ever Fit the Classical Paradigm?

Anthony S. Fauci, M.D.
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland, USA
August 29, 2006

Café Milano, Washington, D.C.

Disclaimer

I promise to you:

The National Institute of Allergy and Infectious Diseases (NIAID) will continue to enthusiastically support the development of an effective preventive vaccine against HIV that will induce "sterilizing immunity" akin to classical viral vaccines.

"Classical Paradigm" of Typical Viral Infections

- Variable courses and sequelae among different infections (e.g. polio, influenza, smallpox); HOWEVER, the vast majority of people recover spontaneously.
- Virus is ultimately cleared and eradicated.
- Protective immunity against subsequent infection is usually complete and often lifelong.

"Paradigm" of HIV Infection

- With few exceptions disease is relentlessly progressive, and virtually no one completely recovers spontaneously.
- Virus is never ultimately cleared and eradicated.
- Protective immunity against subsequent infection does not appear to occur – documented super-infections.

The "Classical Paradigm" for Vaccines Against Viral Infections

- Vaccine is designed to mimic natural infection.
- Protects against infection in the vast majority of vaccinees.
- Immunity is long-lasting.
- Vaccine can serve as a free-standing and sufficient preventative measure.
- Upon field exposure to the microbe, even if initial rounds of replication occur, clinical disease is prevented and the microbe is ultimately eradicated.

Classical Vaccine-Preventable Viral Diseases

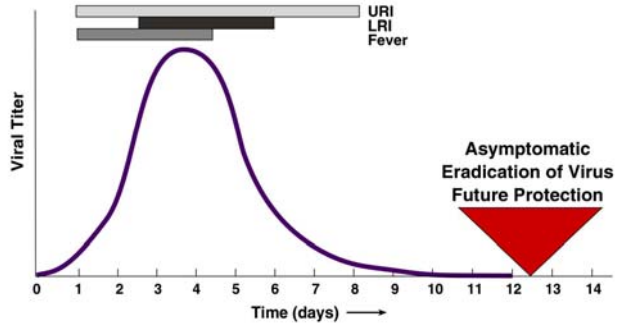
Polio

Smallpox

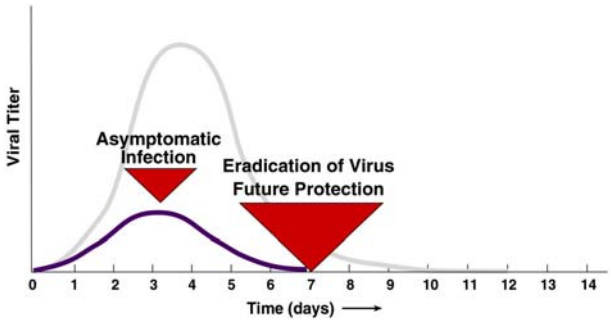
Influenza

Measles

Typical Course of Seasonal Influenza Infection: Non-Vaccinated Individual



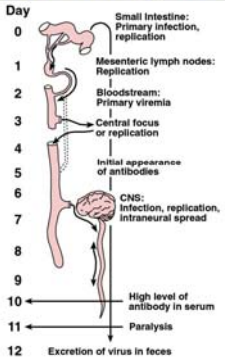
Typical Course of Seasonal Influenza Infection: Vaccinated Individual



Classical Viral Vaccines: A Window of Opportunity for the Immune Response

- With our best classical vaccines, virus neutralized before it reaches its target organ – i.e. there is some level of viral replication, but it is aborted before it causes disease.

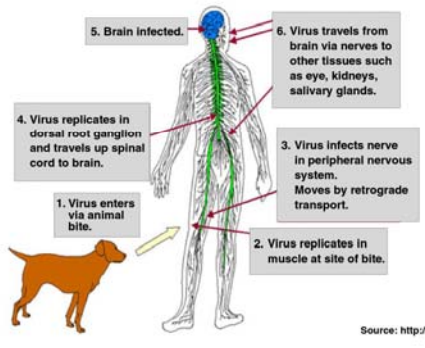
Polio Pathogenesis



- In people with vaccine-induced immunity, polio virus is neutralized before it reaches anterior horn cells in the spinal cord.

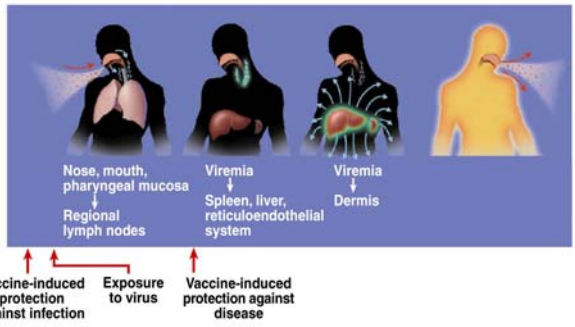
Source: Fields Virology, 4th Edition

Rabies – A Wider Window



Source: http://pathmicro.med.sc.edu

Points Where Smallpox Vaccine Might Induce a Protective Effect



Source: *NEJM* 356:1300, 2002

Typical Viral Vaccines: Classical Outcomes

	Virus		
	Replication	Dissemination	Clearance
Success			
No illness	0	0	Y
No illness	+	0	Y
Mild illness	++	+	Y
Failure			
Frank disease	++++	++++	Y

An HIV Vaccine: Possible Outcomes According to Classical Paradigm

	Virus		
	Replication	Dissemination	Clearance
Success			
No illness	0	0	Y
Failure			
No illness	+	0 or +	N
Mild illness	++	+	N
Frank disease	++++	++++	N

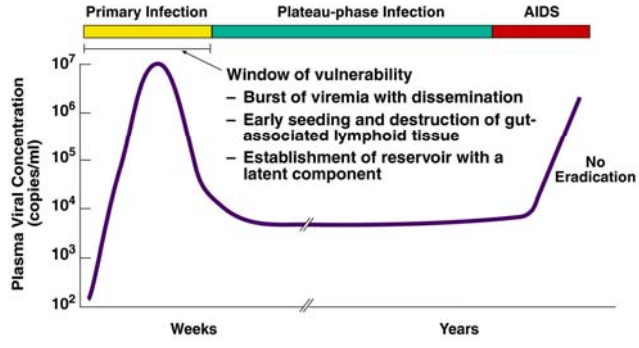
An HIV Vaccine: Possible Outcomes According to Non-Classical Paradigm

	Virus		
	Replication	Dissemination	Clearance
Success			
No illness	0	0	Y
"Partial" Success (Partial Failure)			
No illness	+	0 or +	N
Mild illness	++	+	N
Complete Failure			
Frank disease	++++	++++	N

Early Events in HIV Infection: The Window of Vulnerability

- Burst of viremia with dissemination.
- Early seeding and destruction of gut-associated lymphoid tissue.
- Establishment of a viral reservoir with a latent component.

Course of HIV Infection: Non-Vaccinated Individual



A Burst of Viremia Occurs to Extraordinary Levels in Primary HIV Infection

The New England Journal of Medicine

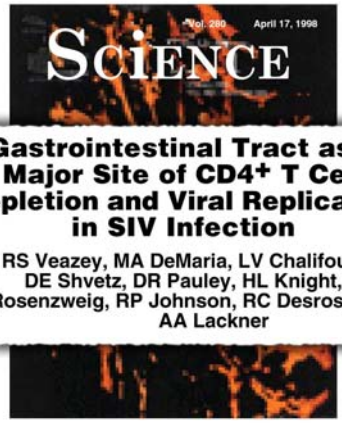
VOLUME 324 April 4, 1991 NUMBER 14

High Titers of Cytopathic Virus in Plasma of Patients with Symptomatic Primary HIV-1 Infection

SJ Clark, MS Saag, WD Decker, S Campbell-Hill, JL Roberson, PJ Veldkamp, JC Kappes, BH Hahn & GM Shaw

Transient High Levels of Viremia in Patients with Primary Human Immunodeficiency Virus Type 1 Infection

ES Daar, T Moudgil, RD Meyer & DD Ho



Gastrointestinal Tract as a Major Site of CD4+ T Cell Depletion and Viral Replication in SIV Infection

RS Veazey, MA DeMaria, LV Chalifoux, DE Shvetz, DR Pauley, HL Knight, M Rosenzweig, RP Johnson, RC Desrosiers & AA Lackner

HIV Rapidly "Guts" the Immune System

nature

Massive Infection and Loss of Memory CD4+ T Cells in Multiple Tissues During Acute SIV Infection

JJ Mattapallil et al.

THE JOURNAL OF EXPERIMENTAL MEDICINE

CD4+ T Cell Depletion During all Stages of HIV Disease Occurs Predominantly in the Gastrointestinal Tract

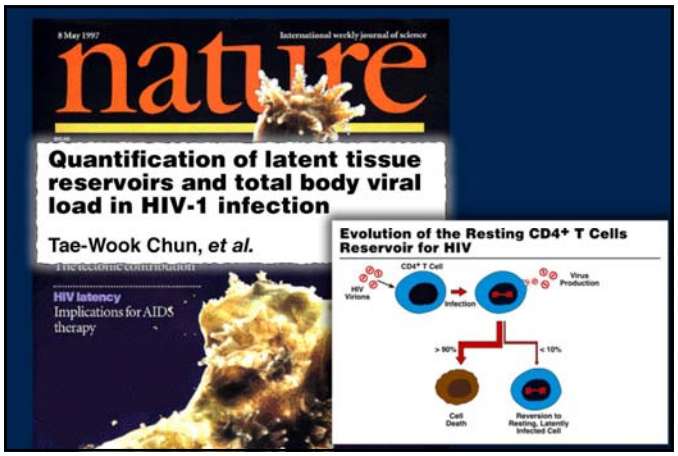
JM Brenchley et al.

Peak SIV Replication in Resting Memory CD4+ T Cells Depletes Gut Lamina Propria CD4+ T cells

Q Li et al.

Primary HIV-1 Infection Is Associated with Preferential Depletion of CD4+ T Lymphocytes from Effector Sites in the Gastrointestinal Tract

S Mehandru et al.



The HIV Reservoir is Established Very Early in the Course of HIV Infection.

Early establishment of a pool of latently infected, resting CD4+ T cells during primary HIV-1 infection

TAE-WOOK CHUN, DELPHINE ENGEL, M. MICHELLE BERREY, THERESA SHEA, LAWRENCE COREY AND ANTHONY S. FAUCI

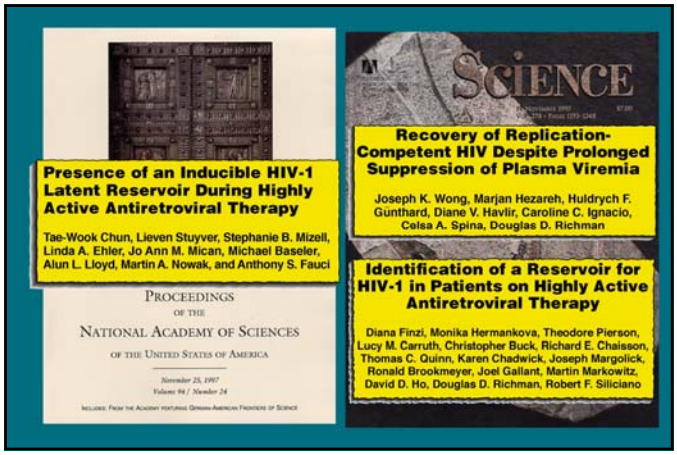
Proceedings of the National Academy of Sciences of the united states of america

July 21, 1998

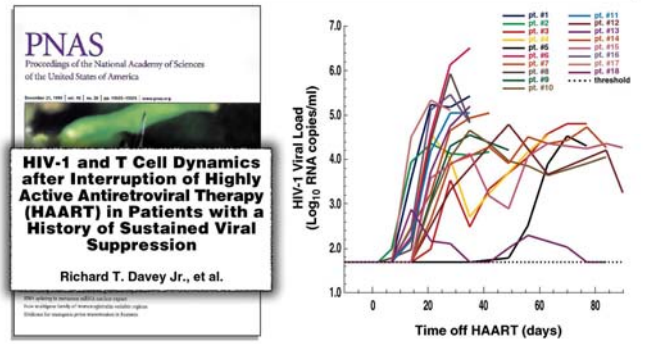
Volume 95 / Number 15

Initiation of HAART in infected individuals as early as 10 days after the onset of symptoms of primary HIV-1 infection did not prevent generation of latently infected, resting CD4+ T cells carrying integrated HIV-1 DNA as well as infectious HIV-1 despite the successful control of plasma viremia shortly after institution of HAART.

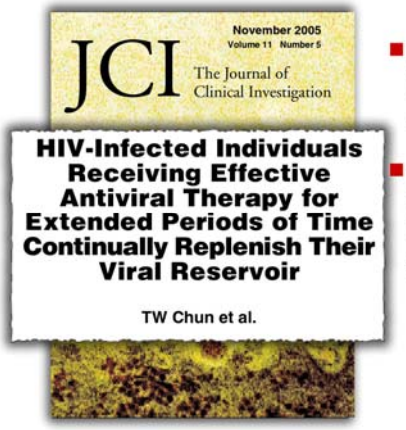
The HIV reservoir is not eradicated even after extended periods of time on therapy and in the absence of detectable viremia.



Rebound of HIV Following Discontinuation of Therapy

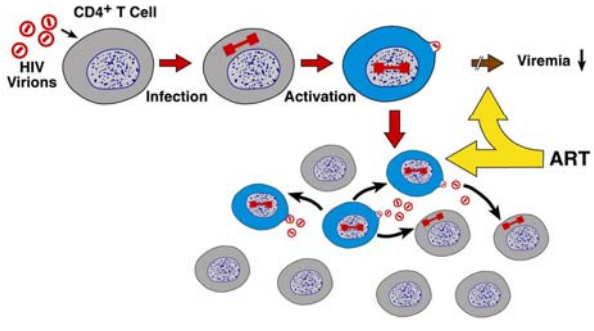


The "Non-Decay" of the HIV Reservoir: Evidence for Continuous Replenishment of the Pool

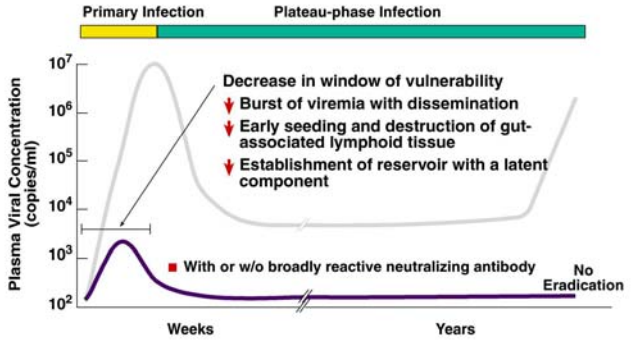


- Replication-competent HIV found in CD4+ T cells despite clinically effective ART for up to 9.1 years.
- Cross-infection between the resting and activated CD4+ T cell compartments may allow continual replenishment of the CD4+ T cell reservoir.

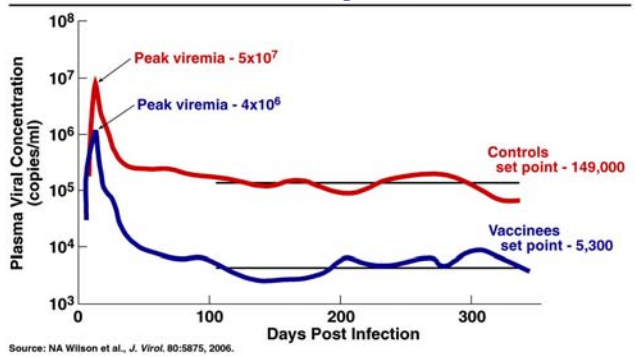
Continuous Replenishment of the CD4+ T Cell Reservoir for HIV Despite Effective ART



Hypothetical Course of HIV Infection: Vaccinated Individual

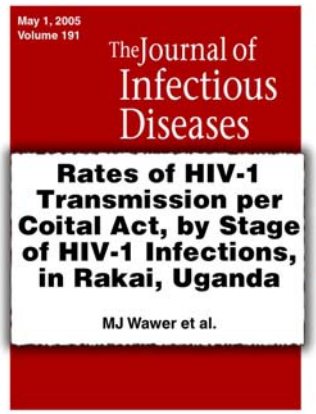


Plasma SIV Concentrations are Lower in Vaccinated Macaques



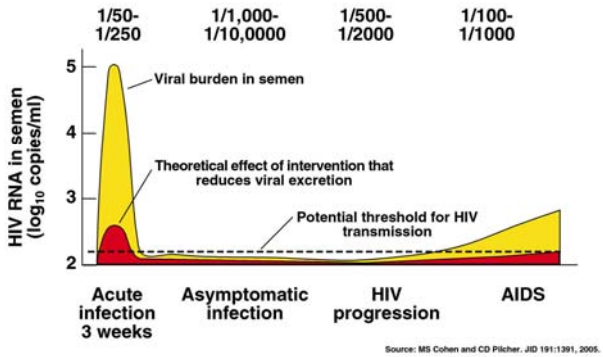
Source: NA Wilson et al., *J. Virol.* 80:5875, 2006.

Vaccine-induced blunting of the initial burst of viremia in acute HIV infection and of the viral set point in established infection may result in a decrease in the efficiency of transmissibility of infection.



- After seroconversion of the index partner, the rate of transmission within the first 2.5 months was almost 12-fold higher than that observed in prevalent index couples.
- The rate then increased significantly again ~2 years before the index partner's death.

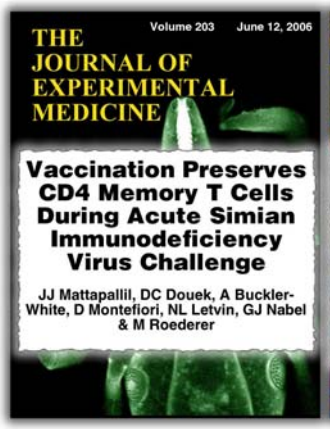
Risk of HIV Transmission Per Coital Act

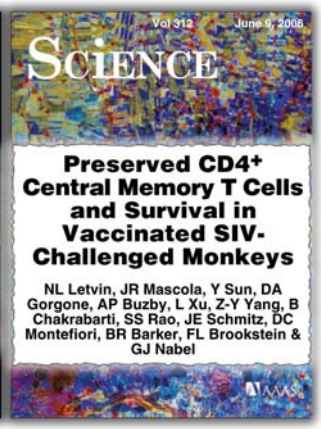


Source: MS Cohen and CD Pilcher. JID 191:1391, 2005.

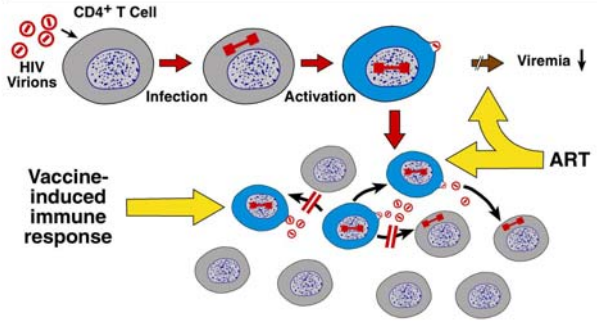
Herd Immunity – The Classical Versus the HIV Paradigm

- **Classical Paradigm** – Vaccinate a critical proportion of people in society such that the infection does not spread widely and so non-vaccinated people are indirectly protected.
- **Potential HIV Paradigm** – Vaccinate people without protecting against infection, but markedly diminishing viral set point lessening the probability of passing on infection to others and so non-vaccinated people are indirectly protected.





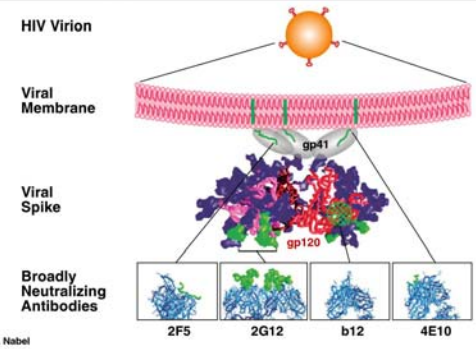
Potential for the Vaccine-Induced Immune Response to Contain the Replenishment of the HIV Reservoir



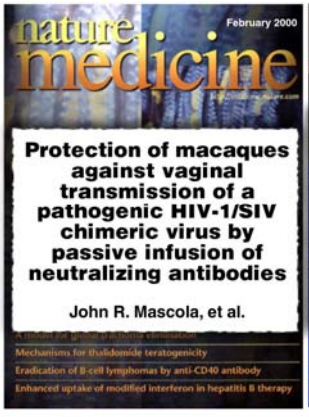
Problems Associated with the Development of Neutralizing Antibodies in Natural HIV Infection and Vaccination

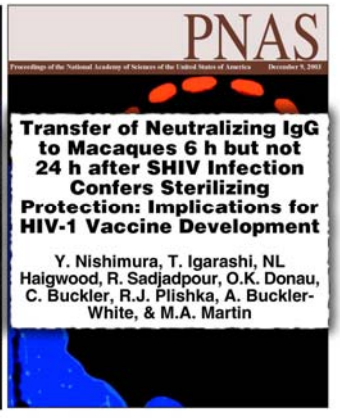
- Lack of exposed neutralizing epitopes to serve as effective immunogens.
- Requirement for high levels of neutralizing antibodies, including at mucosal sites.
- Immune reponse to neutralizing epitopes may be under immunoregulatory control.

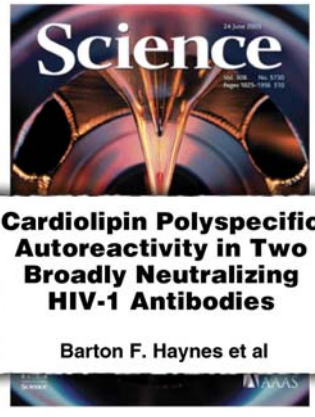
Structures and Targets of Broadly Neutralizing Antibodies for HIV



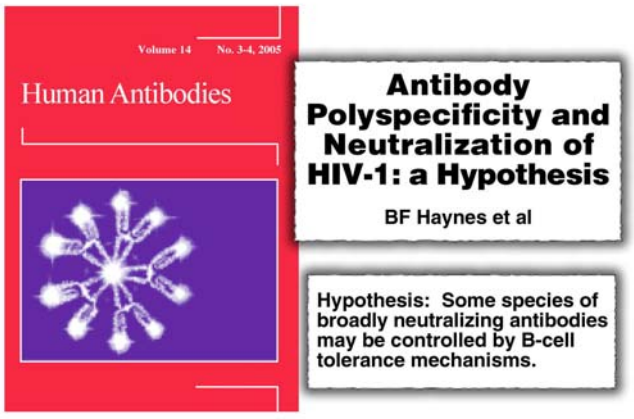
Courtesy of G. Nabel





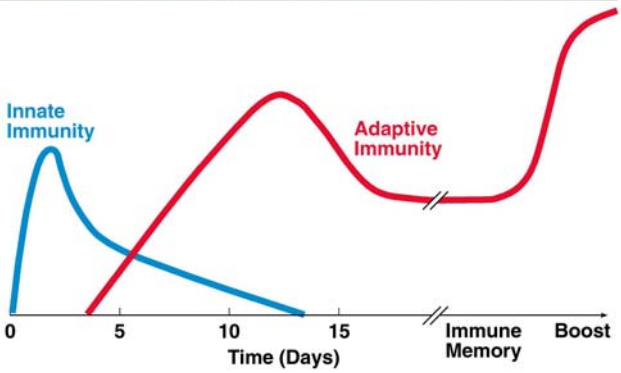


"Here we demonstrate that the two most broadly reactive HIV-1 envelope gp41 human mAbs, 2F5 and 4E10, are polyspecific autoantibodies reactive with the phospholipid cardiolipin."



Closing the Early Window of Vulnerability in HIV Infection: The Potential Role of the Innate Immune System

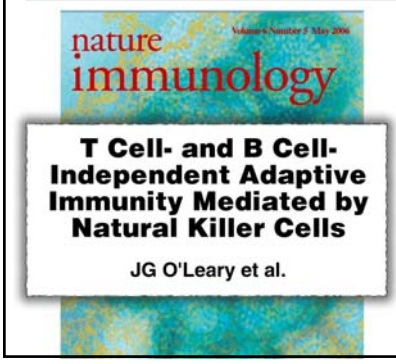
Innate vs. Adaptive Immune Responses



Potential Roles for Innate Immunity in Vaccine-Related Protection Against HIV Infection

- Lessen the gap of vulnerability for establishment of an HIV reservoir during the first days of infection.
- Serve as an adjuvant for the establishment of adaptive immunity in response to the vaccine.

Specific Memory Within the Innate Immune System?



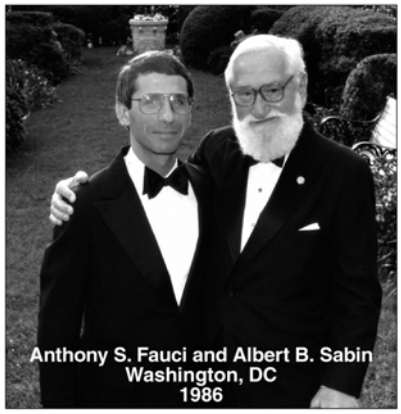
Although the innate immune system can mount adaptive responses in lower animals, this is the first observation of innate immune "memory" in a higher vertebrate (mouse).

The "Classical Paradigm" for Vaccines Against Viral Infections

- Vaccine is designed to mimic natural infection.
- Protects against infection in the vast majority of vaccinees.
- Immunity is long-lasting.
- Vaccine can serve as a free-standing and sufficient preventative measure.
- Upon field exposure to the microbe, even if initial rounds of replication occur, clinical disease is prevented and the microbe is ultimately eradicated.

Approaches to HIV Prevention

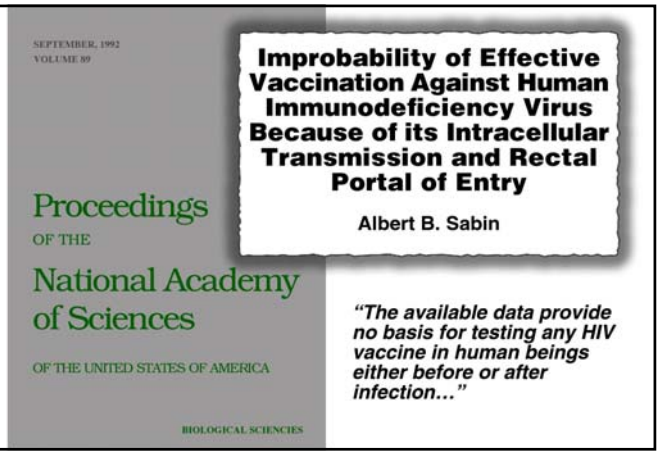
- Education and behavior modification
- Interruption of transmission from mother to child
- Treatment/prevention of drug/alcohol abuse
- Clean syringes (i.e. "needle exchange" programs)
- Circumcision
- Condoms, other barrier methods
- Topical microbicides
- Treatment of other sexually transmitted diseases
- Prophylactic antiretroviral therapy
- **Vaccination**



Anthony S. Fauci and Albert B. Sabin
Washington, DC
1986

"Tony, I do not think we will ever have an HIV vaccine."

Albert B. Sabin
May, 1986



The Way Forward

- An HIV vaccine will almost certainly not fit exactly the "Classical Paradigm" of a viral vaccine. Thus, we are and will be in unchartered waters.
- We must accept this fact, but not let it deter us from an assumption that we, in fact, will be successful in developing a safe and effective HIV vaccine that prevents primary infection or slows disease progression in "vaccine failures."
- The major obstacles are scientific, which means that there are scientific solutions. It is up to us to find them.

Café Milano, Washington, D.C.